Original

Clinical Study of Pneumocystis Carinii Pneumonia as a complication of Immunosuppressive Therapy for Glomerulonephritis

Keiko TAKAHASHI, Ashio YOSHIMURA, Susumu WATANABE, Hiroyuki MORITA and Terukuni IDEURA

Abstract: The aim of this present study was to examine the influence of patient background and therapeutic measures on the prognosis of pneumocystis carinii pneumonia (PCP) occurring as a complication of immunosuppressive therapy for glomerulonephritis. We examined 6 patients that were admitted to our hospital within the last 3 years with PCP while undergoing prednisolone (PSL) therapy for various glomerulonephritides were examined. Diagnoses was IgA nephropathy (n=1), focal segmental glomerulosclerosis (n=1), rapidly progressive glomerulonephritis (n=1), and lupus nephritis (n=3). The study parameters encompassed patient characteristics, PSL administration regimens, the days from PSL administration to pneumonia onset, total dose of PSL preceding the onset of PCP, laboratory data at the onset of symptoms, the intervals from symptom onset to confirmation of PCP on chest X-ray and to the start of therapy, the interval required to determine PCP diagnosis, and finally, the treatment outcomes were studied. All 6 patients were female with a mean age of 53; 4 were older than 60 years. No significant differences were found between surviving cases and fatal cases when comparing doses of PSL administered, tapering regimen of PSL used, or the interval from the onset of PCP symptoms to the appearance of chest X-ray findings or the start of therapy. All patients underwent trimethoprim-sulfamethoxazole therapy, with 3 surviving; 3 of the 4 patients who were older than 60 died. 4) Although levels of lactate dehydrogenase (LDH), β-D glucan, and C-reactive protein (CRP) were all elevated at the onset of symptoms, only LDH was seen to increase earlier, one month prior to the onset of pneumonia. To obtain an early diagnosis of PCP secondary to immunosuppressive therapy, it is important to carefully analyze changes chest X-ray and chest computed tomography changes, as well as to note any increase in LDH and β-D glucan. The administration of PSL in older patients should be performed in combination with the preventive measures against PCP.

Key words: pneumocystis carinii pneumonia, glomerulonephritis, immunosuppressive therapy, preventive treatment

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Introduction

Immunosuppressive therapy is an effective treatment for renal impairment due to chronic glomerulonephritis and collagen vascular diseases. However, such treatment is liable to produce opportunistic infections as a result of diminished cell-mediated immunity.

An example is pneumocystis carinii pneumonia (PCP) for which early diagnosis and immediate treatment may prove lifesaving. The present clinical study was designed to analyze the relationships between both the onset of and prognosis of PCP and factors related to patient background and treatment approaches.

Materials and Methods

Six patients undergoing immunosuppressive therapy for various renal diseases who were diagnosed with PCP were studied. The conditions prompting immunosuppression included IgA nephropathy, focal segmental glomerulosclerosis (FSGS), ANCA associated glomerulonephritis, lupus nephritis, and rapidly progressive glomerulonephritis (RPGN) as listed in Table 1. The treatment regimens included prednisolone (PSL) alone in 5 patients and PSL plus cyclophosphamide in the other patient (Case 2).

Factors investigated for their relationship with pneumonia onset and prognosis included: 1) patient background, 2) schedules of PSL administration, 3) duration (in days) of PSL therapy prior to the first symptoms of PCP, 4) total dose of PSL administered prior to the onset of pneumonia symptoms, 5) laboratory data at the onset of symptoms, 6) interval (in days) between the onset of symptoms and radiographic evidence of PCP on chest X-ray, 7) interval from the onset to the start of PSL therapy, 8) interval (in days) from the first

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnoses prompting immunosuppression</th>
<th>Dose of administered PSL (mg/kg)</th>
<th>Dose of PSL at the onset of symptoms (mg/kg)</th>
<th>Duration of PSL therapy prior to the first symptoms of PCP (days)</th>
<th>Total dose of PSL administered prior to the onset of pneumonia symptoms (mg)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>65</td>
<td>F</td>
<td>FSGS</td>
<td>0.74</td>
<td>0.78</td>
<td>41</td>
<td>1925</td>
</tr>
<tr>
<td>2</td>
<td>38</td>
<td>F</td>
<td>Lupus nephritis (WHO IV type) RPGN</td>
<td>0.86</td>
<td>0.85</td>
<td>66</td>
<td>6980</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>F</td>
<td>Lupus nephritis (WHO III ~ IV type)</td>
<td>1.18</td>
<td>0.83</td>
<td>79</td>
<td>7110</td>
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<td>4</td>
<td>28</td>
<td>F</td>
<td>IgA nephropathy ANCA related glomerulonephritis RPGN</td>
<td>0.76</td>
<td>0.38</td>
<td>66</td>
<td>2210</td>
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<tr>
<td>5</td>
<td>60</td>
<td>F</td>
<td>Lupus nephritis (WHO IV type)</td>
<td>1.15</td>
<td>0.84</td>
<td>138</td>
<td>5150</td>
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<tr>
<td>6</td>
<td>74</td>
<td>F</td>
<td>Lupus nephritis (WHO IV type)</td>
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<td>0.65</td>
<td>40</td>
<td>3050</td>
</tr>
<tr>
<td>Average</td>
<td>53</td>
<td></td>
<td></td>
<td>0.9</td>
<td>0.7</td>
<td>72</td>
<td>4404</td>
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</table>

PSL: prednisolone  
PCP: pneumocystis carinii pneumonia  
FSGS: focal segmental glomerulosclerosis  
RPGN: rapidly progressive glomerulonephritis  
ANCA: anti-neutrophil cytoplasmic antibody
P. Carinii pneumonia and glomerulonephritis

symptoms of PCP to the diagnoses of PCP, and 9) the clinical course after the treatment of PCP.

Results

All 6 patients were female with 4 being older than 60 years (mean age, 53; range, 28–74). The mean daily dose of PSL was 0.9 mg/kg, or approximately 40 to 50 mg/day. The mean duration of PSL therapy preceding the onset of symptoms of PCP was 72 days. At the onset of symptoms, the mean daily dose of PSL was 0.7 mg/kg (approximately 20–45 mg/day) while the mean cumulative dose was 4,404 mg (range 1,925–7,110 mg). There was no statistically significant difference in the cumulative doses of PSL between surviving and dying patients. Four patients (cases 2, 3, 5 and 6) received methylprednisolone pulse therapy for 3 days prior to the onset of PCP symptoms. Case 2 underwent a combined therapy of plasma exchange and 400 mg of cyclophosphamide once a month, while case 5 underwent double filtration plasmapheresis in addition to PSL therapy.

The values of LDH, β-D glucan, and CRP were increased at the onset of PCP in all cases (Table 2). Compared to its value one month prior to PCP symptoms, LDH increased significantly over this period in all cases.

The intervals from the onset of symptoms of PCP to changes on chest X-ray, start of therapy, and definitive diagnosis of PCP were 11, 9, and 24 days, respectively. There was no statistically significant difference between fatal and non-fatal cases with regard to these intervals.

Definitive diagnosis was determined by PCR (DNA amplification) performed on bronchoalveolar lavage (BAL) specimens in all cases except case 3. This case was diagnosed not by chest X-ray, chest computed tomography (CT), and blood tests (LDH, β-D glucan and CRP).

PCP was treated with trimethoprim-sulfamethoxazole in all cases. For all patients (n=6), the crude mortality rate was 50% (3/6) with all 3 deaths occurring in patients older than 60 (3/4 or 75%). Causes of death determined by autopsy included PCP (Case 1) and invasive pulmonary aspergillosis (Case 5). Case 6 was not autopsied and the cause

<table>
<thead>
<tr>
<th>Case No.</th>
<th>LDH before one month at the onset of symptoms (U/l)</th>
<th>Lab data at the onset of symptoms</th>
<th>Interval between the onset of symptoms and radiographic evidence of PCP on chest X-ray (days)</th>
<th>Interval from the onset to the start of PSL therapy (days)</th>
<th>Interval from the first symptoms to the diagnosis of PCP (days)</th>
<th>Outcome</th>
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<td>1</td>
<td>948</td>
<td>1840</td>
<td>7.3</td>
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<td>2</td>
<td>535</td>
<td>608</td>
<td>322</td>
<td>0.5</td>
<td>30</td>
<td>10</td>
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<td>3</td>
<td>864</td>
<td>1276</td>
<td>128</td>
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<td>398</td>
<td>899</td>
<td>305</td>
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<td>708</td>
<td>983</td>
<td>489.8</td>
<td>0.9</td>
<td>11</td>
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<td>6</td>
<td>375</td>
<td>843</td>
<td>19.1</td>
<td>0.8</td>
<td>5</td>
<td>7</td>
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<tr>
<td>Average</td>
<td>638</td>
<td>1105</td>
<td>270.8</td>
<td>4.1</td>
<td>11</td>
<td>9</td>
</tr>
</tbody>
</table>
of death was considered secondary to multiple systemic complications including cytomegalovirus antigenemia, hemophagocytic syndrome, and invasive pulmonary aspergillosis.

Discussion

Incidence rates of PCP reportedly range from 0.01% to 1.3% in immunocompromised hosts receiving anti-tumor therapy, steroids, or immunosuppressive agents for conditions such as leukemia, solid tumors, collagen vascular disorders, or organ transplantation. Although the survival rate of patients with these disorders has improved, the incidence of PCP has increased. The onset of the pneumonia symptoms typically begins 2 to 4 months after the start of steroid therapy, at doses of 30 to 40 mg of PSL/day. Steroid-induced suppression of macrophage activity and cell-mediated immunity is considered the primary factor in pneumocystis carinii infection. In this study, laboratory values suggestive of PCP included an increased serum LDH and β-D glucan, a decreased arterial PO2 on arterial blood gas analysis, and an increased A-a gradient (alveolar-arterial oxygen tension). Radiographic evidence of PCP infection included the appearance of interstitial shadows (ground-glass, nodular, and reticular) radiating from bilateral hila on chest X-ray, a diffusely mottled, ground-glass opacity on chest CT, and the focal accumulation of gallium on scintigram. The definitive diagnosis of PCP was achieved either by performing PCR on BAL and sputum specimens, or, by confirmation of the P. carinii cyst wall and the peculiar parenthesis-like structure of the cyst on Grocott staining.

With early diagnosis and immediate therapy, symptoms from PCP typically resolve within 9–14 days of treatment. However, if effective therapy is postponed for any reason, symptoms will persist and parenchymal lung damage will accumulate. In addition, side effects of curative therapy for PCP may occur as a result of anti-pneumocystis drugs, including super-imposed infections with fungi, other bacteria, or cytomegalovirus, any of which can be fetal. The diagnosis of PCP is often delayed because studies are not always predictive of infection. For example, the chest X-ray is reported to be normal in 12% of cases at the onset of symptoms. Laboratory indices, such as β-D glucan serum levels, are not highly specific for PCP, and co-infection with other pathogens can often not be excluded.

Underlying diseases such as steroid-resistant FSGS, RPGN, and lupus nephritis often require large doses of steroids and PCP is a known complication in patients receiving immunosuppressive therapy for FSGS and RPGN. All of our patients demonstrated increases in LDH, β-D glucan, and CRP levels at the onset of symptoms, however, LDH escalated approximately one month prior to symptom onset. Such an increase should prompt the clinician to perform other studies such as β-D glucan and chest X-ray to confirm the suspicion of PCP allowing early intervention in this immunosuppressed population. In addition, high-resolution CT has been shown to reveal diffuse shadows suggestive of PCP despite a negative chest X-ray in the early stages of infection and may represent a more accurate, non-invasive imaging method in those circumstances. Nevertheless, the present study indicated how extremely difficult the early diagnosis of PCP can be in immunosuppressed patients. Further advances in clinical diagnostics as well as the institution of preventive therapies are necessary. Although not the standard method of preventive treatment, some authors have recommended administration of trimethoprim-
sulfamethoxazole (2 gm by inhalation q.o.d.) or pentamidine (either 300 mg twice monthly by inhalation, or 4 mg/kg i.v. monthly). Preventive drug administration seems especially important in the aged population, who appear by the present study to have a worse prognosis.

The immediate administration of anti-pneumocystis carinii therapy is mandatory when there is clinical suspicion of infection and treatment should continue for about 3 weeks after definite diagnosis by BAL analysis. Drugs included in PCP treatment regimens are trimethoprim-sulfamethoxazole, pentamidine, and steroids, the latter of which is thought to prevent the progression of lung fibrosis due to tissue damage from various cytokines and free radicals\(^{11,12}\).

In conclusion, the early diagnosis of PCP as a complication of immunosuppressive therapy is paramount and requires careful analysis of chest X-rays, chest CT images, and lab values such as LDH and \(\beta\)-D glucan is vitally important. When PSL is administered as immunosuppressive therapy, especially in the older population, clinicians need to secure an early diagnosis of PCP by maintaining an acute awareness of PCP symptoms and proceeding with tests to confirm the diagnosis when suspicions arise. Preventive therapies may also play a crucial role in preventing PCP in this population.

References